PMID: 11056103 [PubMed - indexed for MEDLINE]

☐ **16:** FASEB J 2000 Oct;14(13):2087-96 Related Articles, Links

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VEGF-C and VEGF-D expression in neuroendocrine cells and their receptor, VEGFR-3, in fenestrated blood vessels in human tissues.

Partanen TA, Arola J, Saaristo A, Jussila L, Ora A, Miettinen M, Stacker SA, Achen MG, Alitalo K.

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Recently, vascular endothelial growth factor receptor 3 (VEGFR-3) has been shown to provide a specific marker for lymphatic endothelia in certain human tissues. In this study, we have investigated the expression of VEGFR-3 and its ligands VEGF-C and VEGF-D in fetal and adult tissues. VEGFR-3 was consistently detected in the endothelium of lymphatic vessels such as the thoracic duct, but fenestrated capillaries of several organs including the bone marrow, splenic and hepatic sinusoids, kidney glomeruli and endocrine glands also expressed this receptor. VEGF-C and VEGF-D, which bind both VEGFR-2 and VEGFR-3 were expressed in vascular smooth muscle cells. In addition, intense cytoplasmic staining for VEGF-C was observed in neuroendocrine cells such as the alpha cells of the islets of Langerhans, prolactin secreting cells of the anterior pituitary, adrenal medullary cells, and dispersed neuroendocrine cells of the gastrointestinal tract. VEGF-D was observed in the innermost zone of the adrenal cortex and in certain dispersed neuroendocrine cells. These results suggest that VEGF-C and VEGF-D have a paracrine function and perhaps a role in peptide release from secretory granules of certain neuroendocrine cells to surrounding capillaries.

PMID: 11023993 [PubMed - indexed for MEDLINE]

1: FASEB J 2002 Dec;16(14):1985-7 Related Articles, Links

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Therapeutic lymphangiogenesis with human recombinant VEGF-C.

Szuba A, Skobe M, Karkkainen MJ, Shin WS, Beynet DP, Rockson NB, Dakhil N, Spilman S, Goris ML, Strauss HW, Quertermous T, Alitalo K, Rockson SG.

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Chronic regional impairments of the lymphatic circulation often lead to striking architectural abnormalities in the lymphedematous tissues. Lymphedema is a common, disabling disease that currently lacks a cure. Vascular endothelial growth factors C and D mediate lymphangiogenesis through the VEGFR-3 receptor on lymphatic endothelia. The purpose of this study was to investigate the therapeutic potential for lymphangiogenesis with VEGF-C. We developed a rabbit ear model to simulate human chronic postsurgical lymphatic insufficiency. Successful, sustained surgical ablation of the ear lymphatics was confirmed by water displacement volumetry. After complete healing, the experimental animals (n=8) received a single, s.c. 100 microg dose of VEGF-C in the operated ear; controls (n=8) received normal saline. Radionuclide lymphoscintigraphy was performed to quantitate lymphatic function. Immunohistochemistry (IHC) was performed 7-8 days following treatment. After VEGF-C, there was a quantifiable amelioration of lymphatic function. IHC confirmed a significant increase in lymphatic vascularity, along with reversal of the intense tissue hypercellularity of untreated lymphedema. This study confirms the capacity of a single dose of VEGF-C to induce therapeutic lymphangiogenesis in acquired lymphedema. In addition to improving lymphatic function and vascularity, VEGF-C can apparently reverse the abnormalities in tissue architecture that accompany chronic lymphatic insufficiency.

PMID: 12397087 [PubMed - indexed for MEDLINE]

2: Blood 2003 Jan 1;101(1):168-72 Related Articles, Links

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VEGFR-3 and CD133 identify a population of CD34+ lymphatic/vascular endothelial precursor cells.

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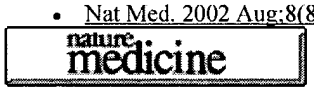
Human CD133 (AC133)(+)CD34(+) stem and progenitor cells derived from fetal liver and from bone marrow and blood incorporate a functional population of circulating endothelial precursor cells. Vascular endothelial growth factor receptor 3 (VEGFR-3) regulates cardiovascular development and physiological and pathological lymphangiogenesis and angiogenesis. However, the origin of VEGFR-3(+) endothelial cells (ECs) and the mechanisms by which these cells contribute to postnatal physiological processes are not known, and the possible existence of VEGFR-3(+) lymphatic or vascular EC progenitors has not been studied. Using monoclonal antibodies to the extracellular domain of VEGFR-3, we show that 11% +/- 1% of CD34(+) cells isolated from human fetal liver, 1.9% +/- 0.8% CD34(+) cells from human cord blood, and 0.2% +/- 0.1% of CD34(+) cells from healthy adult blood donors are positive for VEGFR-3. CD34(+)VEGFR-3(+) cells from fetal liver coexpress the stem/precursor cell marker CD133 (AC133). Because mature ECs do not express CD133, coexpression of VEGFR-3 and CD133 on CD34(+) cells identifies a unique population of stem and progenitor cells. Incubation of isolated CD34(+)VEGFR-3(+) cells in EC growth medium resulted in a strong

proliferation (40-fold in 2 weeks) of nonadherent VEGFR-3(+) cells. Plating of these cells resulted in the formation of adherent VEGFR-3(+)Ac-LDL(+) (Ac-LDL = acetylated low-density lipoprotein) EC monolayers expressing various vascular and lymphatic endothelial-specific surface markers, including CD34, VE-cadherin, CD51/61, CD105, LYVE-1, and podoplanin. These data demonstrate that human CD34(+)CD133(+) cells expressing VEGFR-3 constitute a phenotypically and functionally distinct population of endothelial stem and precursor cells that may play a role in postnatal lymphangiogenesis and/or angiogenesis.

PMID: 12393704 [PubMed - in process]

☐ **3:** Nat Med 2002 Aug;8(8):775-7 Related Articles, Links

Comment on:
- Nat Med. 2002 Aug;8(8):831-40.
- Nat Med. 2002 Aug;8(8):841-9.



VEGF receptor 1 stimulates stem-cell recruitment and new hope for angiogenesis therapies.

Eriksson U, Alitalo K.

Publication Types:
- Comment
- News

PMID: 12152025 [PubMed - indexed for MEDLINE]

☐ **4:** Growth Factors 2002 Jun;20(2):99-107 Related Articles, Links

The angiogenic and lymphangiogenic factor vascular endothelial growth factor-D exhibits a paracrine mode of action in cancer.

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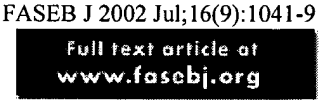
Vascular endothelial growth factor-D (VEGF-D) promotes angiogenesis, lymphangiogenesis and metastatic spread via the lymphatics, however, the mode of VEGF-D action (e.g. paracrine vs. autocrine) was unknown. We analyzed VEGF-D action in human tumors and a mouse model of metastasis. VEGF-D was localized in tumor cells and endothelium in human non-small cell lung carcinoma and breast ductal carcinoma in situ. Tumor vessels positive for VEGF-D were also positive for its receptors, VEGF receptor-2 (VEGFR-2) and/or VEGFR-3 but negative for VEGF-D mRNA, indicating that VEGF-D is secreted by tumor cells and subsequently associates with endothelium via receptor-mediated uptake. The mature form of VEGF-D was detected in tumors demonstrating that VEGF-D is proteolytically processed and bioactive. In a mouse model of metastasis, VEGF-D synthesized in tumor cells became localized on the endothelium and thereby promoted metastatic spread. These data indicate that VEGF-D promotes tumor angiogenesis, lymphangiogenesis and metastatic spread by a paracrine mechanism.

PMID: 12148568 [PubMed - in process]

☐ **5:** FASEB J 2002 Jul;16(9):1041-9 Related Articles, Links



Adenoviral VEGF-C overexpression induces blood vessel enlargement, tortuosity, and leakiness but no sprouting angiogenesis in the skin or mucous membranes.

Saaristo A, Veikkola T, Enholm B, Hytonen M, Arola J, Pajusola K, Turunen P, Jeltsch M, Karkkainen MJ, Kerjaschki D, Bueler H, Yla-Herttuala S, Alitalo K.

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Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) are important regulators of blood and lymphatic vessel growth and vascular permeability. The VEGF-C/VEGFR-3 signaling pathway is crucial for lymphangiogenesis, and heterozygous inactivating missense mutations of the VEGFR-3 gene are associated with hereditary lymphedema. However, VEGF-C can have potent effects on blood vessels because its receptor VEGFR-3 is expressed in certain blood vessels and because the fully processed form of VEGF-C also binds to the VEGFR-2 of blood vessels. To characterize the in vivo effects of VEGF-C on blood and lymphatic vessels, we have overexpressed VEGF-C via adenovirus- and adeno-associated virus-mediated transfection in the skin and respiratory tract of athymic nude mice. This resulted in dose-dependent enlargement and tortuosity of veins, which, along with the collecting lymphatic vessels were found to express VEGFR-2. Expression of angiopoietin 1 blocked the increased leakiness of the blood vessels induced by VEGF-C whereas vessel enlargement and lymphangiogenesis were not affected. However, angiogenic sprouting of new blood vessels was not observed in response to AdVEGF-C or AAV-VEGF-C. These results show that virally produced VEGF-C induces blood vessel changes, including vascular leak, but its angiogenic potency is much reduced compared with VEGF in normal skin.

PMID: 12087065 [PubMed - indexed for MEDLINE]
